1: Free Radic Biol Med. 2005 Jul 1;39(1):71-80. Epub 2005 Apr 14. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Matrix metalloproteinases and free radicals in cerebral ischemia.

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Cerebral ischemia induces a complex series of molecular pathways involving signaling mechanisms, gene transcription, and protein formation. The proteases and free radicals involved are important, both individually and in concert, at each of the steps in the injury cascade. Matrix metalloproteinases (MMPs) and serine proteases are essential in the breakdown of the extracellular matrix around cerebral blood vessels and neurons, and their action leads to opening of the blood-brain barrier, brain edema, hemorrhage, and cell death. Reactive oxygen and nitrogen species affect the signaling pathways that induce the enzymes, the stability of the mRNA, and their activation processes. Mice that either lack MMP genes or overexpress free radical-removing genes exhibit diminished cerebral damage after stroke. Drugs that block MMP activity, or are free radical scavengers, significantly reduce ischemic damage. Understanding the relationship between proteases and free radicals in cerebral ischemia is critical for the design of therapeutic agents aimed at controlling cell death in ischemic tissues.

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AFFIDAVIT

I, Klaus Unsicker, a resident of Heidelberg, Germany, being duly sworn state as follows:

1. I received a Doctor of Medicine from the University of Kiel, Germany. Since 1992 I have been employed at the Ruprecht-Karls-University of Heidelberg. I am currently leader of the Department of Neuroanatomy of the University of Heidelberg and hold the title of Professor of Anatomy & Cell Biology.

   I am the coinventor of US Patent Application 10/009,431 "Neuroprotective properties of GDF-15, a novel member of the TGF-ß superfamily", and author of about 300 publications in several scientific journals.

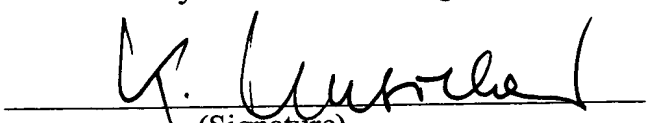
2. With respect to US Patent Application 10/009,431 I herewith confirm as a well known expert of neuronal research:

   I. US Patent Application 10/009,431 teaches a novel method for treating (human) disorders which are characterized by damaged dopaminergic neurons.

   II. The disclosed experimental data comprise a 6-OHDA rotational assay rat model as well as an in vitro model system measuring the effects of iron-intoxication on cultured dopaminergic mesencephalic neurons. In both model systems, GDF-15 has been proven to be an efficient neurotrophic molecule for dopaminergic neurons.

   III. The described experiments are well known and commonly accepted model systems for the testing of novel neurotrophic molecules. If a substance passes these models successfully, it can be reasonably anticipated from persons skilled in the art that this substance will be able to show a protective effect on dopaminergic neurons, even in higher mammals and humans. Such a substance will be a very promising candidate for the treatment of neurodegenerative disorders which are characterized by damaged dopaminergic neurons, particularly for the treatment of parkinson's disease.

WITNESS my hand at Heidelberg, Germany, this 19. day of August, 2005.



(Signature)